BEST AVAILABLE COPY

REMARKS

In the Office Action dated January 13, 2004, the Examiner indicated that claims 52-54 and 104-108 would be allowable if they did not depend from a rejected base claim. Applicants complied with this suggestion in their response of April 14, 2004, in which claims 52 and 104 were re-written in independent form. In a subsequent Office Action, dated July 28, 2004, the Examiner indicated that pending claims 52-54 and 104-108 were **allowed**, but maintained his rejection of other pending claims. In their October 18, 2004 Response, Applicants canceled the rejected claims, and anticipated receiving a Notice of Allowability for claims 52-54 and 104-108.

Prior to mailing the Notice of Allowability for claims 52-54 and 104-108, the Examiner conducted a new prior art search, and located an abstract by Chakmakjian *et al.* from the Journal of Reproductive Medicine. Therefore, despite twice indicating that these claims were allowable, the Examiner now contends that claims 104 and 105 are obvious over the teachings of Chakmakjian.

The Chakmakjian reference is entitled "Bio-availability of Progesterone with Different Modes of Administration," and reports on the bio-availability of micronized progesterone using different formulations and routes of administration. The reference discloses the administration of progesterone **capsules** or **tablets** of 50-200 milligrams **orally**, and the administration of 100 mg of progesterone in a **suppository, vaginally** and **rectally,** during the follicular phase in a group of normally menstruating women. The reference states that all subjects exhibited a significant increase in serum progesterone levels over base line that persisted for at least eight hours and concludes that these findings are in general agreement with previous reports and that oral administration of micronized progesterone could become an attractive alternative to the currently used oral mode of administering synthetic progestins.

Even though there is absolutely no disclosure in the abstract regarding to the method of preparation or of the components of the vaginal progesterone **suppository** administered, the Examiner contends claims 104 and 105 are obvious over Chakmakjian. According to the

Examiner's reasoning, it would have been obvious to make vaginal **tablets** using water, diluents, and excipients from the teachings of Chakmakjian's vaginal **suppository**, and that the order of mixing by switching around the mixing steps provides no patentable significance in the absence of unexpected results.

Applicants emphatically traverse this rejection, for many reasons, including the fact that the abstract indicates that the vaginal and rectal formulations administered in Chakmakjian were **suppositories**. This is in stark contrast to the presently claimed form of administration, which is a **tablet**. The definition of "**suppository**" is as follows:

> A medicated mass adapted for introduction into the rectal, vaginal or urethral orifice of the body, suppository bases are solid at room temperature but melt or dissolve at body temperature.
>
> Commonly used bases are cocoa butter, glycerinated gelatin, hydrogenated vegetable oils, polyethylene glycols of various molecular weights and fatty acid esters of polyethylene glycol.

< http://www.biology-online.org/dictionary/suppository >

By contrast the definition of a "**tablet**" is:

> In pharmacy, a medication, usually mixed with a binder powder, molded and pressed into the form of a tablet, traditionally circular or disk-shaped, but more recently also oblong or differently shaped.

Moreover, as indicated from the definitions, above, the excipients and diluents for a **suppository** are quite different from those of a **tablet**. As indicated in **Exhibit A**, attached, suppository bases are typically comprised oleaginous (fatty) bases such as theobroma oil, cocoa butter, and hydrogenated vegetable oils such as palm, palm kernel, and coconut oil; or water soluble or miscible bases such as glycerinated gelatin, and certain polyethylene glycol polymers.

To the contrary, tablet excipients, such as those in the tablet administered by the presently claimed method, are usually powdered ingredients that are blended with the active ingredient. Such excipients include binders, disintegrants, lubricants, sweeteners, coating agents, and emulsifying agents, comprising starches, microcrystalline and croscarmellose celluloses, hydroxypropylmethyl cellulose, silicone dioxide, talc, fructose, lactose, and mannitol (see **Exhibit B**).

Because they are usually difficult to handle, suppositories are less desirable (and usually more expensive) than tablets.

However, even if there is an obviousness argument, this is rebutted by the evidence of record in this application. The evidence establishes that there is an entirely unexpected result that arises from the mixing sequence of the ingredients in the present invention. That is to say, the micronized progesterone of the invention must first be mixed with water **and no other ingredients**, otherwise, there is an undesirable residue buildup in the vaginas of women receiving the tablet of the invention. This unexpected benefit (avoidance of the residue) is not suggested or disclosed by the prior art, much less Chakmakjian.

Therefore, it is respectfully submitted that no skilled artisan would consider disclosure of a vaginal **suppository** when contemplating making and administering a vaginal **tablet**, and that the tablet of present claims, formed by direct compaction of dry ingredients, is not obvious in view of the teaching of a vaginal suppository. In fact, the reference teaching of administration of a suppository directly teaches away from the present claims, which are directed to administration of a tablet and not a suppository.

To expedite the grant of a patent on the present application, rejected claims 104 and 105 are cancelled, without prejudice, with the intent to pursue them in a divisional application.

In view of the above amendment, the pending application is believed to be in condition for allowance, and this action is earnestly solicited. .

Dated: April 4, 2005

Respectfully submitted,

By _____

Stephanie R. Amoroso, Ph.D.
Registration No.: 51,401
DARBY & DARBY P.C.
P.O. Box 5257
New York, New York 10150-5257
(212) 527-7700
(212) 527-7701 (Fax)
Attorneys/Agents For Applicant

PREPARATION OF SUPPOSITORIES

LEARNING OBJECTIVES

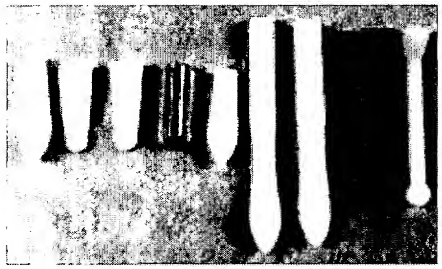
Upon completion of this exercise, the student should be able to:

- List and describe a variety of suppository bases.
- Describe the proper formulation, packaging, and administration of suppository bases.
- Describe three (3) methods of suppository preparation.
- Prepare suppositories by the fusion (molding) technique.
- Determine the density factor of a drug in polyethylene glycol suppositories.

ASSIGNED READINGS

Block, L.H. Medicated Applications, Chapter 90, Suppositories, pp. 1591-1595 in *Remington's*, 19th Ed.

INTRODUCTION



Suppositories are medicated, solid bodies of various sizes and shapes suitable for introduction into body cavities. The medicament is incorporated into a base such as cocoa butter which melts at body temperature, or into one such as glycerinated gelatin or PEG which slowly dissolves in the mucous secretions. Suppositories are suited particularly for producing local action, but may also be used to produce a systemic effect or to exert a mechanical effect to facilitate emptying the lower bowel.

The ideal suppository base should be nontoxic, nonirritating, inert, compatible with medicaments, and easily formed by compression or molding. It should also dissolve or disintegrate in the presence of mucous secretions or melt at body temperature to allow for the release of the medication. As with the ointment bases, suppository base composition plays an important role in both the rate and extent of release of medications.

SUPPOSITORY BASES

Suppository bases may be conveniently classified as according to their composition and physical properties:

- Oleaginous (fatty) bases
- Water soluble or miscible bases

1. Oleaginous Bases include Theobroma Oil and synthetic triglyceride mixtures.

Theobroma Oil or **cocoa butter** is used as a suppository base because, in large measure, it fulfills the requirements of an ideal base. At ordinary room temperatures of 15° to 25°C (59° to 77°F), it is a hard, amorphous solid, but at 30° to 35°C (86° to 95°F), i.e., at body temperature, it melts to a bland,

nonirritating oil. Thus in warm climates, theobroma oil suppositories should be refrigerated.

Particular attention must be given to two factors when preparing suppositories with cocoa butter base. First, this base must not be heated above 35°C (95°F) because cocoa butter is a polymorphic compound and if overheated will convert to a metastable structure that melts in the 25° to 30°C (77° to 86°F) range. Thus, the finished suppositories would melt at room temperature and not be usable.

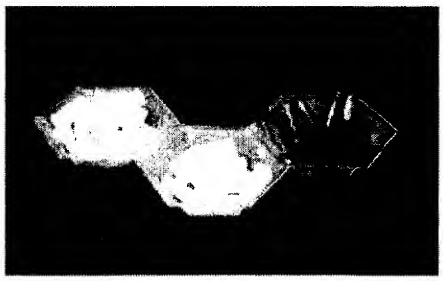
The second factor is the change in melting point caused by adding certain drugs to cocoa butter suppositories. For example, chloral hydrate and phenol tend to lower the melting point. It may be necessary to add spermaceti or beeswax to raise the melting point of finished suppositories back to the desired range.

B. The newer **synthetic triglycerides** consist of hydrogenated vegetable oils. Their advantage over cocoa butter is that they do not exhibit polymorphism. They are, however, more expensive. Some of the bases are single entity formulations. Some of the names may denote a series of bases. In a series, the bases are varied to give a range of melting points. For example, Fattibase® is a single entity base that consists of triglycerides from palm, palm kernel, and coconut oils. Wecobee® is a series of bases. Wecobee FS, M, R, and S are all made from triglycerides of coconut oil. But FS has a melting point range of 39.4 to 40.5°C, M has a range of 33.3 to 36.0°C, R has a range of 33.9 to 35.0°C, and S has a range of 38.0 to 40.5°C. Other triglyceride type bases include Dehydag®, Hydrokote®, Suppocire®, and Witepsol®.

2. Water Soluble/Water Miscible Bases are those containing glycerinated gelatin or the polyethylene glycol (PEG) polymers.

A. **Glycerinated Gelatin** is a useful suppository base, particularly for vaginal suppositories. It is suitable for use with a wide range of medicaments including alkaloids, boric acid, and zinc oxide. Glycerinated gelatin suppositories are translucent, resilient, gelatinous solids that tend to dissolve or disperse slowly in mucous secretions to provide prolonged release of active ingredients.

Suppositories made with glycerinated gelatin must be kept in well-closed containers in a cool place since they will absorb and dissolve in atmospheric moisture. In addition, those intended for extended shelf-life should have a preservative added, such as methylparaben or propylparaben, or a suitable combination of the two. To facilitate administration, glycerinated gelatin suppositories should be dipped in water just before use.



B. **Polyethylene Glycol Polymers** have received much attention as suppository bases in recent years because they possess many desirable properties. They are chemically stable, nonirritating, miscible with water and mucous secretions, and can be formulated, either by molding or compression, in a wide range of hardness and melting point. Like glycerinated gelatin, they do not melt at body temperature, but dissolve to provide a more prolonged release than theobroma oil.

Certain polyethylene glycol polymers may be used singly as suppository bases but, more commonly, formulas call for compounds of two or more molecular weights mixed in various proportions as needed to yield a finished product of satisfactory hardness and dissolution time.

Since the water miscible suppositories dissolve in body fluids and need not be formulated to melt at body temperature, they can be formulated with much higher melting points and thus may be safely stored at room temperature.

Examples of various PEGs used in suppository bases are:

1450 30% 8000 70%	1450 1.96 gm 3350 200 mg	300 60% 8000 40%	300 48% 6000 52%
1000 95% 3350 5%	1000 75% 3350 25%	300 10% 1540 65% 3350 25%	Silica Gel 25 mg PEG 1450 2.3 gm

METHODS OF PREPARATION

Suppositories can be extemporaneously prepared by one of three methods.

1. Hand Rolling is the oldest and simplest method of suppository preparation and may be used when only a few suppositories are to be prepared in a cocoa butter base. It has the advantage of avoiding the necessity of heating the cocoa butter. A plastic-like mass is prepared by triturating grated cocoa butter and active ingredients in a mortar. The mass is formed into a ball in the palm of the hands, then rolled into a uniform cylinder with a large spatula or small flat board on a pill tile. The cylinder is then cut into the appropriate number of pieces which are rolled on one end to produce a conical shape.

Effective hand rolling requires considerable practice and skill. The suppository "pipe" or cylinder tends to crack or hollow in the center, especially when the mass is insufficiently kneaded and softened.

2. Compression Molding is a method of preparing suppositories from a mixed mass of grated suppository base and medicaments which is forced into a special compression mold. The method requires that the capacity of the molds first be determined by compressing a small amount of the base into the dies and weighing the finished suppositories. When active ingredients are added, it is necessary to omit a portion of the suppository base, based on the density factors of the active ingredients.

3. Fusion Molding involves first melting the suppository base, and then dispersing or dissolving the drug in the melted base. The mixture is removed from the heat and poured into a suppository mold. When the mixture has congealed, the suppositories are removed from the mold. The fusion method can be used with all types of suppositories and must be used with most of them.

Learn all about using suppository molds and packaging

Suppositories are generally made from solid ingredients and drugs which are measured by weight. When they are mixed, melted, and poured into suppository mold cavities, they occupy a volume – the volume of the mold cavity. Since the components are measured by weight but compounded by volume, density calculations and mold calibrations are required to provide accurate doses.

When a drug is placed in a suppository base, it will displace an amount of base as a function of its density. If the drug has the same density as the base, it will displace an equivalent weight of the base. If the density of the drug is greater than that of the base, it will displace a proportionally smaller weight of the base. Density factors for common drugs in cocoa butter are available in standard reference texts. The density factor is used to determine how much of a base will be displaced by a drug. The relationship is:

$$\text{Density Factor} = \frac{\text{weight of drug}}{\text{weight of base displaced}}$$

For example, aspirin has a density factor in cocoa butter of 1.3 (*see Remington's*). If a suppository is to contain 0.3 g of aspirin, it will replace 0.3 g ÷ 1.3 or 0.23 g of cocoa butter. If the blank suppository (suppository without the drug) weighed 2 g, then 2 g - 0.23 g or 1.77 g of cocoa butter will be needed for each suppository, and the suppository will weigh 1.77 g + 0.3 g = 2.07 g. So if a pharmacist was making 12 aspirin suppositories using cocoa butter as the base, he would weigh 1.77 g × 12 or 21.24 g of cocoa butter and 0.3 g × 12 or 3.6 g of aspirin.

The weight of the blank suppository is easily determined. A portion of the suppository base is melted, poured into the suppository mold and allowed to congeal. The suppositories are removed from the mold, and the total weight of the suppositories is determined. The average weight of the blank suppository is determined by dividing the total weight by the number of suppositories.

Some example density factors of drugs in cocoa butter are shown in the table below (*see Remington's*):

Aspirin	1.3
Barbital	1.2
Bismuth salicylate	4.5
Chloral hydrate	1.3
Cocaine hydrochloride	1.3
Codeine phosphate	1.1
Diphenhydramine hydrochloride	1.3
Morphine hydrochloride	1.6
Phenobarbital	1.2
Zinc Oxide	4.0

When the Density Factor is Not Known

When bases other than cocoa butter are used, or when the density factor for a drug in cocoa butter is not known, then the density factor can be **estimated by calculation** or experimentally determined by the **double casting technique**.

Estimation by Calculation

One method to determine the density factor of a drug in a base other than cocoa butter requires the use of the ratio of a blank suppository of the non-cocoa butter base to a blank suppository of the cocoa butter base. This information is generally obtained by calibrating the mold first with one base and then the other base.

As an example of the method, a mold was calibrated with the PEG base and the average blank suppository weighed 2.24 grams. The same mold was calibrated with cocoa butter and those blank suppositories weighed 1.87 grams on average. Therefore, the ratio of the two weights was:

$$\frac{\text{weight of PEG suppositories}}{\text{weight of cocoa butter suppositories}} = \frac{2.24\ \text{g}}{1.87\ \text{g}} = 1.20$$

If 200 mg of aspirin is to be incorporated into each PEG suppository, it is necessary to determine how much PEG base will be displaced by the aspirin. That displacement amount can be calculated as follows:

- density factor of aspirin in cocoa butter = 1.3 (from reference sources)
- density of PEG base relative to cocoa butter = 1.20 (the ratio obtained from the calibrations)
- 0.2 g of aspirin will displace $\frac{0.2\ \text{g}}{1.3} \times 1.20 = 0.18\ \text{g}$ of PEG base

For each PEG suppository to be formulated, 0.2 g of aspirin and 2.06 g (2.24 - 0.18 g = 2.06) of the PEG base will be needed.

Double Casting Technique

The total quantity of drug is mixed with an amount of base which is inadequate to fill the number of cavities. The mixture is poured into the mold, partially filling each cavity, and the remaining portion of the cavities are filled with the melted blank base. The cooled suppositories are then removed, remelted, mixed, and recast to evenly distribute the active ingredient. By recording the necessary information, the pharmacist can determine the weight of base displaced by the drug and then calculate the density factor.

Note: a portion of the formula will be lost during this process, so you should always prepare for 2 extra suppositories to ensure that you have enough mixture for the desired number of suppositories.

Sample calculation of density factor

Using a particular mold, the average weight of a plain cocoa butter suppository was found to be 2.0 g. Using the same mold, cocoa butter suppositories, each containing 300 mg of drug A, were found to weigh 2.1 g each. So,

weight of suppository of cocoa butter = 2.0 g
weight of drug in each medicated suppository = 0.3 g
weight of suppository with drug and cocoa butter = 2.1 g
weight of base in medicated suppository = 2.1 g - 0.3 g = 1.8 g
weight of base displaced = 2.0 g - 1.8 g = 0.2 g

Therefore, density factor of drug A = 0.3 g ÷ 0.2 g = 1.5

Now, knowing the density factor for the drug, the pharmacist can make calculations for a batch of suppositories. To prepare 10 suppositories:

weight of drug A needed = 10 suppositories × 300 mg/suppository = 3000 mg = 3.0 g
weight of base needed for plain suppositories = 10 suppositories × 2.0 g/suppository = 20.0 g
weight of base displaced by 3 g drug A = 3.0 g ÷ 1.5 = 2.0 g
weight of base needed for medicated suppositories = 20.0 g - 2.0 g = 18.0 g

Copyright © 1996-2005, R.P. Shrewsbury
All rights reserved.

HOME
Lab Home

HEALTH SCIENCES

Disclaimer: The information provided in this technical bulletin is strictly educatic intended as medical advice. For diagnosis and treatment of medical disorders, c health care professional. This information may be copied and freely distributed c remains intact and unchanged.

Tablet Excipients

Technical Background

Excipients are inactive, non-medicinal ingredients that are used by all manufact tableted products to impart desirable characteristics important for manufacture, of use, and product efficacy. Most are powdered materials that are blended with ingredients prior to tableting. Excipients may be classified as follows according t general function.

- **Binders** are added to hold a tablet together after it has been compresse binders, tablets would break down into their component powders during p shipping, and routine handling.
- **Disintegrants** are used to ensure that, when a tablet is ingested, it breal the stomach quickly into its fine powder form. Rapid disintegration is a ne step in ensuring that the active ingredients are bioavailable and readily al
- **Lubricants** are required during manufacture to ensure that the tableting the raw ingredient blend) does not stick to the pressing equipment. Lubri improve the flow of powder mixes through the presses, and they help fini release from the equipment with a minimum of friction and breakage.
- **Sweetening and Flavoring Agents** are commonly added to chewable ta formulations to improve taste, texture and overall palatability.
- **Coating Agents** are used to impart a finished look and a smooth surface and to mask any unpleasant flavors that the tablet ingredients may have. agents are applied after tablet pressing in a separate operation.
- **Emulsifying agents** are widely used as dispersing, suspending and clar agents. They are used to stabilize blends of liquids that are not mutually improve the bioavailability of some lipid-soluble compounds.

Excipients Used in USANA's Nutritional Tablets

Several excipients are used in USANA tablet formulations. They are selected fo inertness, non-toxicity and contribution to the overall integrity and performance product. All have excellent safety profiles and meet the requirements of the U.S

Pharmacopeia guidelines. Many serve multiple functions (e.g. disintegrant and l are "high performance" meaning that minimal amounts can be added to achieve effects. Descriptions of each follow.

- **Starch and Pregelatinized Starch** are used primarily as binders to impr durability and integrity. Both are derived from corn. Pregelatinized starch hydrolyzed and dried to make it flow better during tableting. It also has su binding characteristics. Starch and pregelatinized starch are also used as disintegrants. After ingestion, these starch granules swell in the fluid envi the stomach and force the tablet to break apart.
- **Microcrystalline Cellulose** serves multiple functions in tablet formulas. excellent binder and disintegrant. It is derived from plant fiber.
- **Croscarmellose Sodium** is called a "super disintegrant" because it is ve even at very low concentrations at promoting the breakdown of tablets fo ingestion. It is manufactured from cellulose (plant fiber) which has been p have a high affinity for water.
- **Fumed Silica** is an extremely fine form of silicon dioxide. (Silicon dioxide naturally as quartz or sand.) It is a white powdery material that is used in to promote flow of tableting powders and to prevent their sticking in table also promotes tablet disintegration.
- **Talc**, a natural magnesium silicate mineral, is a fine white powder that, lik silica, is used as a tableting lubricant and flow agent.
- **Ascorbyl Palmitate** is used primarily as a lubricant to improve the flow c powders in the presses during manufacture and to facilitate ejection of ta the equipment following compression. While more costly than standard lu ascorbyl palmitate, which is a fat-soluble form of vitamin C, also provides additional vitamin C activity.
- **Fructose and Mannitol** are used in Kids Chooables as sweetening ager the unpleasant taste of vitamins and help improve the texture. Both are n sweeteners extracted and purified from plant sources, particularly from fr addition, these ingredients have good binding properties and aid in tablet and integrity.
- **Hydroxypropyl Methylcellulose** is used as a film-coating agent on all U tablets except Kids Choo-ables. As its name implies, this excipient is deri cellulose or plant fiber.
- **Carnauba Wax** is a constituent of the film-coating agent on all USANA ta Kids Chooables. It is a natural wax which helps protect the tablets and ai ease of swallowing the tablets.
- **Maltodextrin**, which is derived from the partial hydrolysis of starch, is an constituent of the film-coating agent on all USANA tablets except Kids Ch
- **Polysorbate 80, Polyethylene Glycol 400 , Propylene Glycol, Sorbita Monooleate, and Plasdone** function as lipophilic emulsifiers, stabilizers suspending agents to improve the solubility of CoQ10 in USANA's CoQu These ingredients are commonly used in the pharmaceutical industry in c counter and prescription medicines, in the cosmetic industry in thousands cosmetic products, and in the food industry as components of beverages goods and frozen desserts. All have well documented long-term safety pr pose no health hazard at the levels used for such products under conditio manufacturing practice.

© 1998, USANA, Inc. All rights reserved. 06/98

Copyright © 2004 Usana Health Sciences, Inc.

This Page is Inserted by IFW Indexing and Scanning Operations and is not part of the Official Record

BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ BLACK BORDERS
- ☐ IMAGE CUT OFF AT TOP, BOTTOM OR SIDES
- ☐ FADED TEXT OR DRAWING
- ☐ BLURRED OR ILLEGIBLE TEXT OR DRAWING
- ☐ SKEWED/SLANTED IMAGES
- ☐ COLOR OR BLACK AND WHITE PHOTOGRAPHS
- ☐ GRAY SCALE DOCUMENTS
- ☐ LINES OR MARKS ON ORIGINAL DOCUMENT
- ☐ REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY
- ☐ OTHER: _____

IMAGES ARE BEST AVAILABLE COPY.
As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.